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Review

Tramadol deaths in Northern Ireland: A review of cases from 1996 to 2012

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ABSTRACT

In the UK tramadol is a frequently prescribed opioid analgesic which is becoming increasingly popular as a drug of misuse. Its use varies worldwide and in the last decade it has been upgraded to a controlled substance in several countries, due to an increased number of deaths associated with its use.

A review of all deaths associated with tramadol in Northern Ireland was performed and this highlighted 127 cases from 1996 to the end of 2012. A 10% increase in deaths due to tramadol was noted. In 2001 tramadol deaths represented 9% of all drug misuse deaths rising to 40% in 2011. The majority of the deaths occurred in males (62%), with a median age of 41 years, living in the Belfast city area (36%). Tramadol fatalities were found in combination with other drugs/medicines (49%), alcohol (36%) or alone (23%). Most of those who died did not reach hospital, with only 2% presenting with multi-organ or acute liver failure. In just over half of the deaths tramadol had not been prescribed by a medical practitioner (53%). Depression, addiction and seizures were recognised risk factors.

An increase in awareness of tramadol toxicity is needed amongst the public and doctors.

1. Introduction

Tramadol was first introduced in Germany in the late 1970's.[1] Currently widely prescribed in the United Kingdom, it has yet to be classified as a controlled drug as defined by the Misuse of Drugs Act, 1971. Worldwide, tramadol's availability varies greatly. It can be freely purchased over the counter in Kuwait and Thailand without prescription. In the last decade Australia, Sweden and some states of America have changed their classification of tramadol to a controlled substance in response to an increased number of deaths associated with its use.

In recent decades, there has been an increase in the prescription of opioid analgesics and a rise in the use of addiction services by opioid addicts in the UK.[2,3] There is growing concern amongst some practitioners regarding the potential for an opioid epidemic similar to that seen in the United States of America.[4,5] However, despite a recent reduction in the overall number of opioid deaths in the UK, there continues to be an increase in tramadol prescriptions and number of tramadol related deaths.[2,6] The increase in tramadol prescriptions can largely be attributed to the phased withdrawal of co-proxamol (dextropropoxyphene and paracetamol) between 2005–2008.[7] Many practitioners believe that it has fewer risks including less potential for misuse, less dependence and fewer occurrences of respiratory depression than other opioids, as stated in the current edition of the British National Formulary.[8] The BNF does not, however, highlight the euphoric effects of tramadol, similar to those seen with morphine, heroin and oxycontin and as tramadol is more readily available than these controlled drugs, it is becoming an increasingly popular drug of abuse.

Tramadol is an opioid analgesic with similar effects to codeine.[9] It is a weak agonist at μ-opioid central receptors in the brain. Furthermore, tramadol also inhibits the re-uptake of noradrenaline and serotonin. In practice this is supported by only a partial reversal of its actions by naloxone, the opiate reversal agent used in the treatment of respiratory depression.[10]

Tramadol is well-absorbed orally and reaches its peak effects within 2 h and has a half-life of approximately six hours.[9] It is metabolised in the liver, by N- and O-demethylation via the cytochrome P450 pathway, followed by conjugation, before finally being excreted by the kidneys. The active metabolite, O-desmethlytramadol (M1), is largely responsible for tramadol's analgesic effects, and therefore toxic effects, as it has a significantly greater affinity for central opioid receptors than the parent drug.[11] Furthermore, any drug interactions with the cytochrome P450 enzymes, will therefore interfere with tramadol metabolism and alter its concentration in blood and tissue samples.[12]

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The side-effects of tramadol are varied with the most significant being neurological rather than cardiovascular. Symptoms are usually seen within four hours of ingestion.[10] Nausea, tachycardia and hypertension have been reported starting at doses of 500 mg.[10] At doses greater than 800 mg coma and respiratory depression may occur.[10] Respiratory depression, though uncommon, is more likely to arise when tramadol is taken in combination with alcohol or other central nervous system (CNS) depressants. Seizures are more common with tramadol than other opioids, occurring at doses as low as 200 mg.[13] The risk of seizures is greatest in those with a known seizure disorder.[14] The "serotonin syndrome" is another recognised side-effect of tramadol. This syndrome includes non-specific symptoms of agitation, tachycardia, confusion and hypertension.[15,16] These may occur with tramadol usage alone but are more likely to be fatal when taken in combination with other drugs which also increase serotonin activity particularly selective serotonin re-uptake inhibitors (SSRI's), mono-amine oxidase inhibitors (MAOI's) and tricyclic anti-depressants (TCA's).[14,15] Seizures and the serotonin syndrome are thought to be due to tramadol's ability to inhibit the re-uptake of serotonin and nor-adrenaline. These symptoms may also occur with other opioids which also weakly inhibit serotonin re-uptake (e.g. fentanyl, pethidine, methadone and dextromethorphan).[17] The lowest fatal dose reported to cause cardiac arrest and death was 5000 mg, between 12 and 50 times the daily dose.[18]

Side-effects may be more common in the elderly as they are more likely to be on numerous other medications.[14] In cases of suspected poisoning, measurement of blood tramadol levels in hospital is not usually carried out. The recommended management is supportive care. Most symptoms, if not life-threatening, usually resolve within 24 h.[13,14]

2. Methods

A review was performed of all autopsy reports in the State Pathologist's Department, Northern Ireland, where tramadol poisoning was included in the cause of death given by the pathologist. The case details were collected from the computerised Case Management System or retrieved from the archives. The total number of such deaths was 127 from 1996 to the end of 2012.

3. Results

The first death was reported in 1996. There has been a gradual increase in tramadol deaths during the last decade, from 2 cases in 2001 to 19 in 2012. The highest number occurred in 2011 when there were 23 deaths (Fig. 1).

In 2001 tramadol deaths represented 9% of deaths due to drug misuse in Northern Ireland. This rose to 40% in 2011 (Fig. 2).

More than half of the deaths were male (63% compared to 38% female). The average age at death was 41 years. The youngest death occurred in a fifteen year old girl and the oldest in an 80 year old female. The largest age group for male deaths was 21–30 years and for females 41–50 years. Overall the 41–50 age group gave the largest number of tramadol deaths (Fig. 3).

The majority of cases came from the Belfast area (36%), the capital city of Northern Ireland with a population of approximately 300,000 inhabitants. Outside of Belfast, the remaining province was split by healthcare sectors into north (24% of the cases), east (17% of the cases), south and west (each 10% of the cases) and 2% were from visitors (Fig. 4).

In the majority of cases death occurred at home or in the community. Only 8 patients (6%) reached hospital. Three of these hospital deaths were associated with multi-organ or liver failure.

In 24 cases (20%) tramadol was implicated indirectly or as a contributory factor in the cause of death. These deaths were principally due to aspiration pneumonia (17 cases). Others included drowning (2), positional asphyxia (1), bowel obstruction (1), congestive cardiac failure due to cardiomegaly (1), emphysema (1) and haemorrhage due to an incised radial artery (1).

Tramadol was prescribed in only 46% of cases (58), as recorded on the clinical summary provided at the time of autopsy. In 53% of the cases (67) tramadol was not prescribed and in 1% of cases (2) the source of the tramadol was unknown.

Only 29 deaths (23%) were due to ingestion of tramadol alone. In this group there was no variation in age or sex, however there was a higher percentage of apparently deliberate overdoses. The remaining deaths were due to tramadol in combination with other drugs and/or alcohol. Alcohol was associated with 36 deaths (28%). Tramadol was most commonly fatal when used in combination with one other drug, the most common being diazepam.

In 80 deaths (63%) there was a history of depression with a further 49 deaths (39%) admitting to previous overdose or self-harm. Sixty-three deaths (50%) were recorded as suffering with chronic pain, 52 deaths (41%) were known to abuse alcohol or drugs and 19 deaths (15%) had mental health problems. Only 7 cases (6%) had a diagnosis of epilepsy. One case had a witnessed seizure prior to death, which was associated with a fatal level of tramadol in

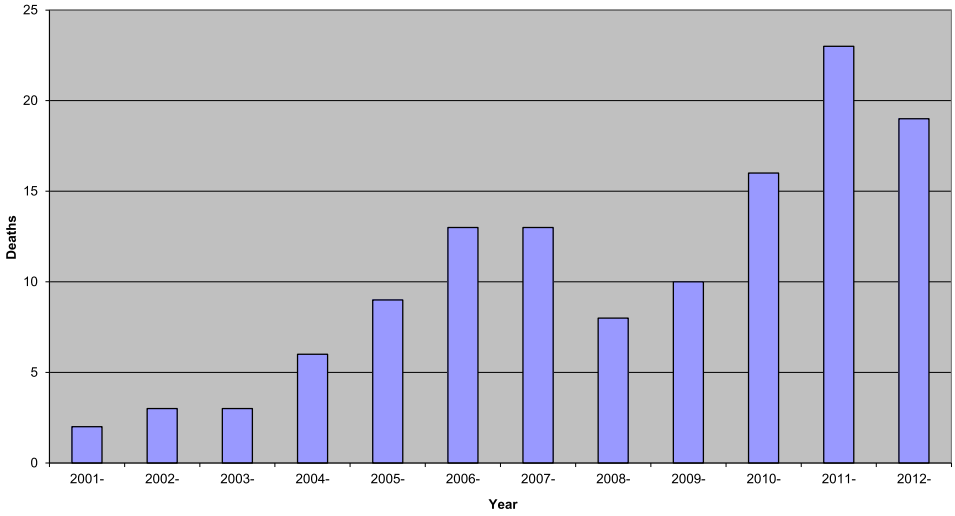

Fig. 1. Total number of tramadol deaths per year from 2001 to 2012.

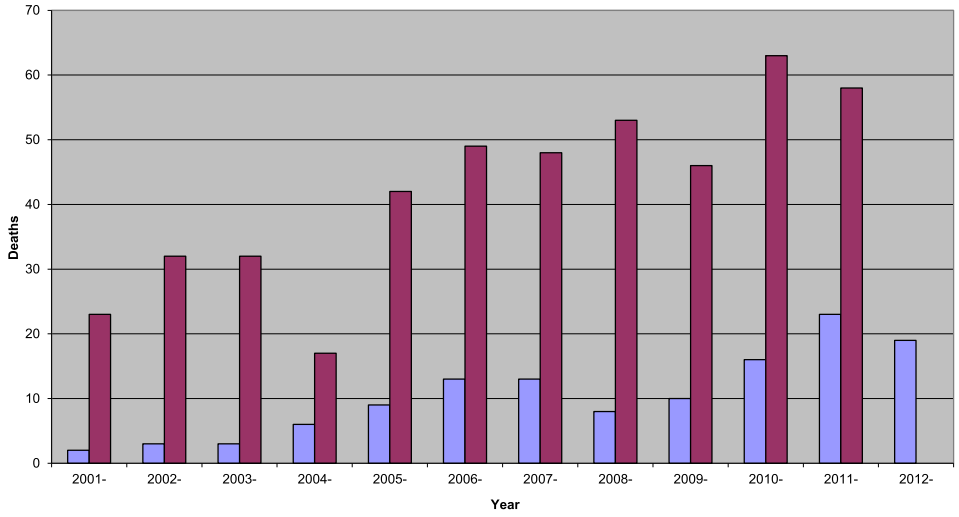

Fig. 2. Tramadol deaths compared to all drug misuse deaths in Northern Ireland.

combination with venlafaxine, an antidepressant with similar properties to tramadol.

The manner of death in 48 deaths (38%) was deemed most likely to be suicide, as indicated by a suicide note, empty blister packs or a verbal confession. Thirty-four deaths (27%) were thought to be accidental whilst the intentions of the remaining 45 deaths (35%) were unknown.

The highest recorded blood serum level of tramadol where it alone caused death was 88.8 mg/L, almost 45 times greater than the fatal level. The lowest level was 1.85 mg/L. The fatal range of tramadol when taken in combination with other medications or drugs was considerably lower, ranging from 0.15 to 39 mg/L.

4. Discussion

The first death due to tramadol toxicity dealt with by the State Pathologist's Department was recorded in 1996. This correlates with cases reported in the literature at about this time.[19] The 10% rise in tramadol deaths seen in Northern Ireland corresponds with similar rises seen in the rest of the UK[20,21] and worldwide.[22–24] In our review of cases tramadol deaths were most common in males aged between 21 and 30 years old and females aged between 41 and 50 years old. The average age of death was 41 years old, similar to the median age of 39 for all deaths due to drug misuse in Northern Ireland.[25] Most tramadol deaths were seen in the Belfast area (36%). This is likely to reflect the higher population in this area and possibly an increased availability and higher level of drug misuse.

Slightly more than half of deaths were due to non-prescribed usage of tramadol. A difference was noted in the average ages of the prescribed and the non-prescribed groups. The average age of death in non-prescribed cases was 37 years compared to 45 in prescribed cases. A similar younger age group was also seen in non-prescribed methadone-related deaths compared to prescribed cases.[26]

Death from tramadol usage is most commonly seen in combination with other medications, drugs and/or alcohol, with reported post-mortem levels of tramadol in peripheral blood ranging from 1.4 to 23 mg/L, similar to levels recorded in our study.[11,13,15] The lower levels seen in our cases overlap with levels one might expect to see in therapeutic doses (0.1–0.8 mg/L). Conversely studies have also shown fatal levels of tramadol in the living arrested for disorderly driving.[15,27] Fewer cases of tramadol overdose alone

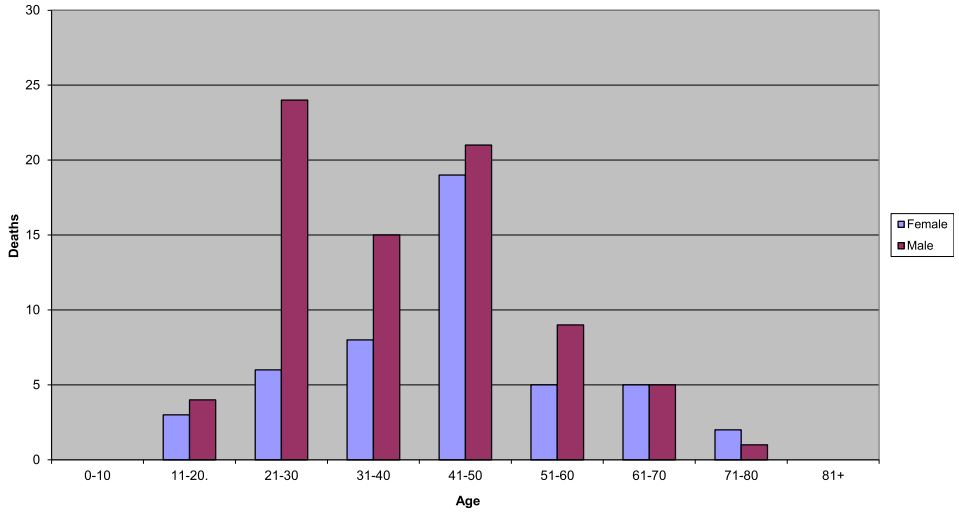

Fig. 3. Tramadol deaths by sex and age group.

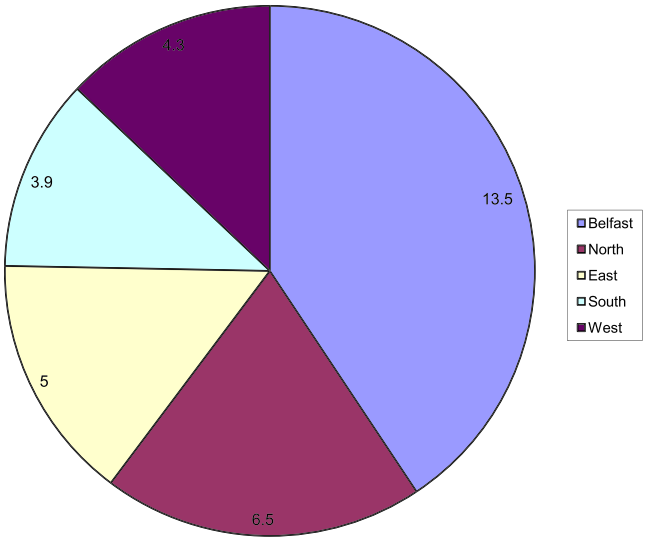

Fig. 4. Tramadol deaths per 100,000 population in Northern Ireland.

have been reported.[11,28–30] In our review only four cases (3%) were noted where just tramadol was detected in the blood. In this group, we noted the highest level of tramadol, 88.8 mg/L and a higher range of fatal levels of blood tramadol compared to tramadol taken in combination. Significantly higher blood tramadol levels may be reached if there is significant opioid tolerance or a slow accumulation of the active metabolite, O-desmethyltramadol (M1), due to diversion of tramadol metabolism to the non-active form, N-desmethyltramadol (M2), resulting in a slower death.[19,30] If the ratio of metabolites favours the active form (M1:M2 > 1) a quicker death has been suggested.[19,30] Unfortunately, the tramadol metabolites are not quantified in our laboratory to utilise these ratios. Alcohol was found to be a contributory factor in 28% of deaths. Alcohol is a central nervous system depressant and in combination with other CNS depressants, including tramadol, can synergistically be fatal. In these cases, the levels of tramadol detected may not necessarily be fatal on their own but may result in death when combined with high or moderately high blood alcohol concentrations.

Acute liver failure is an uncommon but a reported feature of tramadol overdose.[11,31] This presentation was seen in 3 cases and confirmed histologically after post-mortem examination.

Depression, addiction and known seizure history appear to be risk factors for tramadol related deaths. Tramadol can lower the seizure threshold.[32] There was one case of seizure prior to death possibly related to tramadol and venlafaxine co-administration.

5. Conclusion

Tramadol deaths have risen significantly in Northern Ireland in the last decade. The Advisory Council on the Misuse of Drugs for England and Wales have recently reviewed the rise in tramadol deaths and published their recommendations.[33] These include the upgrade of tramadol to a Class C drug as defined by the Misuse of Drugs Act 1971 and for it to be listed under Schedule III of the Misuse of Drugs Regulations 2001 to allow more control of the drug and to help reduce its misuse.

Manufacturers of tramadol have previously produced “Dear Healthcare Professional” letters to warn prescribers of the risks of addiction and effects of co-administration with alcohol, tranquilisers and anti-depressants.[34] However, despite this, only a small and insignificant change in prescribing patterns has been documented.[14]

Few cases of tramadol poisoning reach hospital or are detected clinically. Therefore it is important to highlight the growing problem of tramadol abuse to the public and to general practitioners. A large number of tramadol deaths may be unintentional and the drug may be obtained by non-prescribed means. Support and training should be offered to those prescribing tramadol on its adverse effects, its dual mechanism of action and special care should be taken when prescribing to those known to suffer from depression, seizures, addiction or suicidal ideation. The risks of co-administration with SRI’s, MAOI’s, CNS depressants and alcohol also need to be addressed to highlight the potential risk of fatalities at lower levels than those associated with tramadol only poisonings.

Ethical approval

None.

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Conflict of interest

None declared.

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